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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/662,061

09/12/2003

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EXAMINER

GAMBEL, PHILLIP

ART UNIT

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No. 10/662,061	Applicant(s) HORVATH ET AL.	
	Examiner Phillip Gambel	Art Unit 1644	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 27 September 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3,5-8,12,14,16,18,22,23 and 34-39 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,5-8,12,14,16,18,22,23 and 34-39 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/ are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

1. Applicant's amendment, filed 09/28/2007, has been entered.

Claims 5, 6 and 12 have been amended.

Claims 4, 9, 11, 13, 15, 17, 19-21 and 24-33 have been canceled previously.

Claims 1-3, 5-8, 12, 14, 16, 18, 22, 23 and 34-39 are pending.

Applicant's election of an anti-CD18 antibody that inhibits binding of ICAM-1 as the first therapeutic agent (E); the species of anti-CCR2 antibody that inhibits binding of MCP-1 as the second therapeutic agent (H); and angioplasty as the species of vascular procedure has been acknowledged.

Claims 1-3, 5-8, 12, 14, 16, 18, 22, 23 and 34-39 read on the elected invention and are under consideration in the instant application.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Action will be in response to applicant's arguments, filed 09/28/2007.

Given applicant's Remarks and the Statement of Common Ownership, filed 09/28/2007, that the LaRosa (U.S. Patent No. 6,312,689) (1449; #AH3) is prior art only under 35 USC § 102(e)(2) and that this patent and the instant applications were commonly owned or subject to an obligation of assignment to the same persons at the time the claimed invention was made,

the previous rejection under 35 USC 103(a) has been withdrawn.

New Grounds of Rejection under 35 USC § 103(a) have been made herein.

3. Upon reconsideration of applicant's amended claims, the previous rejection under 35 U.S.C. § 112, second paragraph, with respect to the recitation of "adhesion molecule antagonist" and "antagonist of CCR2 function" has been withdrawn.

4. Claims 1-3, 5-8, 12, 14, 16, 18, 22, 23 and 34-39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rogers et al. (US 2002/0006401) and Furukawa et al. (Circ. Res. 84:306-314, 199 (1449; #AY2) in view of Lind et al. (US Pat. No. 6,084,075) (1449; #AB)

and in further view of Daugherty et al. (U.S. Patent No. 6,797,492), Strom et al. ( in Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456) and the well known recombinant techniques to produce recombinant antibodies known and practiced at the time the invention was made as acknowledged on pages 16-20 of the instant specification of record.

The claims are drawn to methods of inhibiting stenosis or restenosis of a blood vessel following a vascular intervention therapy, including angioplasty involving placement of a stent, by administering both an antibody to the CD18 component of a  $\beta 2$  integrin and an antibody to CCR2.

The teachings of Rogers et al. (US 2002/0006401) in view of Daugherty et al. (U.S. Patent No. 6,797,492), Strom et al. ( in Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456) and the well known recombinant techniques to produce recombinant antibodies known and practiced at the time the invention was made as acknowledged on pages 16-20 of the instant specification are of record and reiterated herein.

The teachings of Furukawa et al. in view of Lind et al. have been provided to address the use of CCR2-specific antibodies in the claimed methods at the time the invention was made.

Furukawa et al. teach that MCP-1 (a CC chemokine) promotes neointimal hyperplasia in early neointimal lesion formation, and that neutralization of MCP-1 with antibody before and immediately after arterial injury was effective in preventing restenosis after angioplasty (see entire document, especially Abstract).

Furukawa et al. conclude that while their results suggest MCP-1 may have additional effects; neutralization of MCP-1, particularly in humans, is critical to blocking development of intimal hyperplasia by reducing the accumulation of monocytes (mononuclear cells) in the neointimal lesion after angioplasty (e.g., see page 312, 1<sup>st</sup> column).

Furukawa et al. do not teach administering antibodies to the chemokine receptor CCR2 to inhibit stenosis or restenosis of a blood vessel following a vascular intervention therapy, including angioplasty involving placement of a stent per se.

Lind et al. teach and claim antibodies, including chimeric antibodies, that antagonize the function of the CC chemokine MCP-1 by binding to the MCP-1 receptor, CCR2 (see entire document, especially Abstract and Claims).

Lind et al. also teach that MCP-1 upregulates CD11b/CD18, thereby facilitating trans-endothelial cell migration (e.g., see column 3, especially lines 22-27).

Lind et al. review that MCP-1 plays an important role in atherosclerosis (a form of primary stenosis) by actively recruiting monocytes to the lesion (e.g., column 2, especially lines 16-30).

It would have been obvious to the ordinary artisan at the time the invention was made to substitute an anti-CCR2 antibody, and particularly a chimeric anti-CCR2 antibody, as taught by Lind et al. for the anti-MCP-1 antibody taught by Furukawa et al.

The ordinary artisan would have been motivated to make such a substitution in view of the art-recognized desirability of substituting chimeric or humanized antibodies for rodent antibodies for administration to humans.

Therefore, the given the teachings of the references as a whole, the ordinary artisan would have recognized that adhesion and/or recruitment of cells to the site of vascular injury (e.g., after the vascular intervention procedure angioplasty) is an early and requisite event in neointimal hyperplasia that leads to restenosis of the vessel.

Rogers et al. teach that antibody inhibition of the integrin MAC-1 (CD11b/CD18) is beneficial in reducing neointimal hyperplasia via inhibition of both neutrophil and leukocyte (mononuclear cell) recruitment to the lesion.

Both Furukawa et al. and Lind et al. teach that neutralization of the MCP-1/CCR2 interaction is beneficial in inhibiting monocyte accumulation in vascular lesions.

Lind et al. also review that CCR2 upregulates CD11b/CD18; thus the ordinary artisan at the time the invention was made would have recognized that CCR2 and CD11b/CD18 are two critical components in the early accumulation of neutrophils and mononuclear cells (including the mononuclear cell types of leukocytes and monocytes) at sites of vascular injury which promotes neointimal hyperplasia leading to restenosis.

Blockade of each pathway by antibody therapy is taught by the references to reduce neointimal hyperplasia after vascular injury in animal models of restenosis.

The following of record is reiterated for applicant's convenience.

Rogers et al. teach methods of inhibiting stenosis or restenosis, which results by vascular surgery, including angioplasty and stents (e.g. see Abstract and Background of the Invention and paragraphs [0070] – [0075] ), with integrin antagonists, including CD18-specific antagonists and LFA-1-specific antibodies (e.g., see paragraphs [0013], [0026], [0031] – [0032], [0033]-[0038] ) (see entire document, including Background of the Invention, Summary of the Invention, Detailed Description of the Invention and Claims).

Note that LFA-1 was a known CD11a/CD18 integrin that binds ICAM-1 (CD54).

Alternatively, CD18-specific antagonists, including the IB4 anti-CD18 antibody specificity was known at the time the invention was made, as taught by Daugherty et al. (see entire document). In addition to the teachings of humanizing the IB4 antibody (see entire document), Daugherty et al. also teach the known use of anti-CD18 antibodies in inhibiting the influx and migration of leukocytes expressing CD18 (see columns 12-13, overlapping paragraph).

In addition to the teachings above, it was known at the time the invention was made that the use of immunosuppressive therapy relies upon a number of basic principles as set forth in Strom et al. These principles include that different agents are used, each of which is directed at a different molecular target and aimed at interrupting several discrete stages in the immune activation pathway (e.g. see page 451 and Figure 36.1). Also, additive-synergistic effects are achieved through the application of each agent at a relatively low dose, thereby limiting the toxicity of each individual agents while increasing the total immunosuppressive effect (see page 451, column 1, paragraph 2).

Recombinant techniques to produce recombinant antibodies known and practiced at the time the invention was made as acknowledged on pages 16-20 of the instant specification.

In addition, Daugherty et al. teach recombinant means of producing humanized antibodies of interest, including anti-CD18 antibodies (see entire document).

Also, newly added Lind et al. provides for the use of therapeutic recombinant antibodies by the ordinary artisan at the time the invention was made.

The ordinary artisan was motivated to employ recombinant antibodies such as humanized antibodies in therapeutic regimens to take advantage of recombinant means of producing homogeneous antibodies of interest as well as to diminish immunogenicity of therapeutic antibodies in human therapeutic regimens.

Given the teachings by Rogers et al. and newly added Furukawa et al. in view of Lind et al. as well as the well known practice of combination therapy in immunosuppression, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ both anti-CCR2 antibodies and anti-adhesion molecule antibodies, given the expressed teachings to treat stenosis and restenosis with said antagonists at the time the invention was made.

It was prima facie obvious to combine two compositions (humanized antibodies to CD18 and chimeric antibodies to CCR2), each of which is taught by the prior art to be useful for the same purpose (inhibition of restenosis by reduction of neointimal hyperplasia), in order to form a third composition that is to be used for the very same purpose; the idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Further, given the teachings of Rogers et al. that targeting the early step of cell adhesion is particularly desirable because it reduces redundant (and therefore difficult to block) downstream mechanisms; the ordinary artisan would have been particularly motivated to combine two reagents that each act early to block initial recruitment and/or adhesion of the different cell types to the injured vessel.

In addition, combination therapy using the humanized anti-CD18 antibody and antibodies to other surface molecules is explicitly taught by Waldmann et al.

The ordinary artisan would have had a reasonable expectation that the combination of the anti-CD18 and anti-CCR2 antibodies would have at least the same, if not a greater, ability to inhibit restenosis following vascular injury.

Finally, the ordinary artisan at the time the invention was made would have recognized that a method inhibiting neointimal hyperplasia would be equally applicable in methods of inhibiting stenosis or restenosis induced by any of a variety of insults/injuries to a blood vessel, including percutaneous transluminal coronary angioplasty or other vascular intervention procedures such as angioplasty including placement of a stent. In each case the vascular injury results in neointimal hyperplasia which eventually leads to restenosis. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. See MPEP 2144.06. Further, Strom et al. provides the known motivation and expectation of success, including additive and synergistic results, in combining immunosuppressants targeting discrete molecular targets, as well as limiting the toxicity of immunosuppression.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

5. The terminal disclaimer filed on 09/28/2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,663,863 (1449; #A9) has been reviewed and is accepted. The terminal disclaimer has been recorded.

6. No claim is allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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January 22, 2008